of neuroectodermal origin.--

--98. (Amended) The method of claim 92 or 94, wherein the administering is effected at two or more sites.--

--99. (Amended) The method of claim 98, wherein the administering is effected at three sites.--

REMARKS

Claims 78-99 are pending in the subject application. Applicants have hereinabove canceled claim 93 without disclaimer or prejudice to their right to pursue the subject matter of this claim in a later-filed application. Applicants have also amended claims 94-96 and 98-99. This amendment does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 78-92 and 94-99 will be pending.

Objection to Figure 6B

The Examination stated that the prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No. 9). The Examiner stated that applicants stated that they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner stated until applicants submit a proper figure said objection is maintained.

In response, applicants will provide a new figure 6B upon the indication of allowable subject matter.

Obviousness-type, double patenting

The Examiner provisionally rejected claims 78-99 under the judicially created doctrine of obviousness-type, double patenting as being unpatentable over the claims 78-100 of copending Application No. 08/475/784 for reasons already made of record in Paper No. 23, mailed 10-5-99. The Examiner stated that applicants assert that the added new claims in the copending application obviate the obvious type double patenting. The Examiner stated that applicants' assertion is not persuasive since the claims of the instant application encompass conjugating the ceramide portion of GM2 via a variety of linkages to keyhole limpet hemocyanin (KLH) as recited the claims in copending application. The Examiner stated that applicants' amendments are insufficient to remove the rejection. The Examiner stated even if applicants limited the '784 application ro remove GD2, it is noted that the conjugation of other gangliosides would be obvious over the each other because they all have similar base structure and are derived from GM3 as indicated by Ritter et al (Cancer Biology, 1991) of record.

The Examiner provisionally rejected claims 79-99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44 and 46-56 of copending Application No. 08/477,147 for reasons already made of record in Paper No. 23, mailed 10-5-99. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Actions. The Examiner stated that applicants' amendments are insufficient to overcome the double patenting rejection in regard to 08/477,147.

The Examiner provisionally rejected claims 79-99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 97-118 of copending application no. 08/196,154 for reasons already made of record in Paper No. 23, mailed 10-5-99. The Examiner stated that the instantly claimed compositions drawn to specific species of gangliosides conjugated to KLH by a specific C-4 bond (see claim 79) anticipate the claims of 08/196,154. The Examiner stated that applicants' assertion that the amendment to the claims obviates the double patenting rejection is not persuasive.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claims of the cited applications do not render obvious the claims of the subject application and therefore, an obviousness-type double patenting rejection is not appropriate. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 93-99 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons for reasons made of record in Paper No. 16, mailed 7-11-97. The Examiner stated that applicants' arguments have been carefully considered but are not persuasive. The Examiner stated that applicants argue that the conjugate vaccine of the invention prevents outgrowth of micrometastases and prevents cancer *per se* (Zhang et al, Cancer

Research 58:2844-2849, 1998). The Examiner stated that this is not persuasive, the claims are not drawn to preventing outgrowth of micrometastases and the conjugate used in the paper is GD2-KLH (10 ug of GD2 conjugated to 60 ug KLH, wherein the conjugation of GD2 to KLH was achieved by conversion of the GD2 ceramide double bond to aldehyde by ozonolysis and attachment to KLH by reductive amination in the presence of cyanoborohydride) plus 10 ug QS-21. The Examiner stated thus, the conjugate of the claims is not that which has been demonstrated by the art prevents outgrowth of micrometastases, nor does the method provide for the method of the paper (multiple doses administered by a specific route. The Examiner stated that moreover, the article specifically teaches that the vaccine "...should be used exclusively in the adjuvant setting, where circulating tumor cells and micrometastases are the primary targets (page 2844, last line of abstract)." The Examiner stated that the evidence of the paper targeted circulating cells specific type of tumor cell (lymphoma) which was administered intravenously and micrometastases thereof from circulation, which is clearly not representative of cancers or relapses as instantly claimed. The Examiner stated moreover, Figure 1, demonstrates that administration of the GD2-KLH, QS-21 vaccine at days -21, -14 and -7 does not prevent cancer as demonstrated by death of some of the experimental group after experimental intravenous challenge of lymphoma cells (see Figure 1, Experiments 3 and 6B). The Examiner stated at page 2845, column 2, second and third paragraph, Zhang et al teach that the vaccine prolonged survival, but in the discussion of experiment 6, only 4 out of 6 vaccinated mice remained disease free at the latest time point measured. The Examiner stated moreover, Zhang et al admit that the alleged protection in Experiment 7 of Figure 1, was "not statistically significant" and

moreover this experiment is not directly comparable with the other experiments because the tumor burden administered intravenously was substantially reduced. The Examiner stated clearly the vaccine when administered prior to the cancer does not prevent as claimed or as argued by applicants. The Examiner stated additionally, prevention of relapse as claimed has not been demonstrated nor specifically addressed by this paper and Zhang et al admits that "If antibodies of sufficient titer and potency to eliminate circulating cancer cells and micrometastases could be maintained in cancer patients as well, even metastic cancer would have quite a different implication. The Examiner stated with continuing showers of metastases no longer possible, aggressive treatment of primary and metastatic sites might result in long term control." The Examiner stated that relapsing of cancer is quite different than elimination of micrometastases and the paper only addresses circulating syngeneic tumor lymphoma cells and micrometastases (see page 2848, column 1, last paragraph) not primary cancer. Zhang et al do not address primary cancer and the experimental protocols set forth therein do not address prevention of primary cancer as is claimed for prevention of relapse of cancer. The Examiner stated reduction of circulating lymphoma cells and reduction in micrometastases is not commensurate in scope with prevention of cancer or prevention of a relapse of cancer. The Examiner stated the rejection is maintained.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 93 without disclaimer or prejudice to their right to pursue the

subject matter of this claim in a later-filed application. The claims no longer recite a "method of preventing relapse of a cancer." Applicants have also hereinabove amended claim 94 such that it no longer recites "preventing." Applicants contend that these amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 53-77 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. The Examiner stated that this a new matter rejection. The Examiner stated applicants point to a variety of pages to support the invention claiming "altered ceramide portion". As previously set forth, applicants' disclosure provides for a single means of conjugating the ceramide of gangliosides to KLH, by means of the passage at page 32, lines 13-18 which provide for a specific coupling procedure at the C-4 carbon of the sphingosine moiety of the ceramide to the ε-aminolysyl group of a proteins (ozonolysis, production of a functional aldehyde group and coupling to an ε-aminolysyl group on a protein by reductive amination). The Examiner stated that the passage at page 12, lines 22-26 in combination with the passage at page 32, lines 13-18 does not support a broad coupling to any generic portion of the ceramide backbone of the ganglioside, by a generic means by cleavage of any double bond (i.e. C=O and coupling by any linkage process or any

generic alteration). The Examiner stated the specification does not support by way of written description, convey that applicants had at the time of filing broadly contemplated any means of altering the ceramide, any means of coupling or broadly any alteration of the ceramide portion of the ganglioside, a concept that is now broadly claimed. The Examiner stated applicants' specification provide for a single means as set forth above. The Examiner stated no generic contemplation of conjunction was contemplated nor generic alteration of the ceramide portion were contemplated at the time of filing. The Examiner stated applicants' were still clearly not in possession of that which is now broadly claimed. The Examiner stated correction is required. The Examiner stated that applicants' amendments are insufficient to obviate this rejection.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully remind the Examiner that the subject rejection is a written description rejection. Applicants submit that the application sufficiently describes the claimed invention such that it is clear that they were in possession of the claimed invention as the time the application was filed. In support, applicants respectfully direct the Examiner's attention to page 32, lines 1-30, and specifically to line 14 which states "via its **ceramide** portion" [emphasis added]. Accordingly, the written description requirement is satisfied.

Applicants respectfully point out that claims 53-77 are no longer pending. In the response filed April 5, 2000, applicants canceled claims 53-77 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed

application and added new claims 78-99. Accordingly, it does not appear that the Examiner's comments are directed to claims 78-99. Again, applicants contend that the application sufficiently supports the currently pending claims, i.e. claims 78-92 and 94-99. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 78-94 and 96-99 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S.Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al. (The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:98-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is maintained for reasons made of record for claims 53-66 and 68-77 in paper No. 23, mailed 10-5-99 and reiterated below. The Examiner stated that Livingston et al (Cancer Research) teach a composition administered to melanoma patients for stimulation the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (page 7046-7048). The Examiner stated that Livingston et al teach that the composition for treatment is administered at a concentrations of 100, 200, or 300 ug with an adjuvant, Bacillus-Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p 7046, column 1, paragraph 3, and paragraph bridging p 7046-47). The Examiner stated that Livingston et al

teach that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). The Examiner stated that Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). The Examiner stated that Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). The Examiner stated that Livingston et al differ by not teaching the conjugation of the GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on Keyhole Limpet Hemocyanin (KLH) in a composition for treatment. The Examiner stated that Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). The Examiner stated that Ritter et al teaches discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization. The Examiner stated that Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group bearing glass beads. The Examiner stated that Ritter et al (1990) teach that GD3 lactone

is more immunogenic than GD3. The Examiner stated that Livingston et al (U.S. Patent No. 5,102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28). The Examiner stated that Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino acid group of aminoethyl agarose or the amino group bearing glass beads. The Examiner stated that Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 3). The Examiner stated Marciani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1). The Examiner stated that Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies. The Examiner stated it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Livingston et al by conjugating the GM-2 to KLH by covalently coupling GM2 to KLH by substituting GM2 for the globoside and KLH for the aminoethyl agarose to produce a GM-2-KLH conjugate by means of the olefinic bond of the sphingosine moiety of the GM2 (i.e. the instant ceramide double bond) and the ε-aminolysyl groups present in the KLH protein using the method of

Liane et al and add QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages by Ritter et al (1991) and adding the QS-21 would be advantageous because it provides for a higher antibody response that the commonly used adjuvant use by Kensil et al and QS-21 provides the advantages that it is not toxic to animals as is taught by Marciani et al. The Examiner stated it also would have been *prima facie* obvious to use doses of between 10 and 80 ug of QS-21 in the composition and optimize the dose accordingly because the immune response with QS-21 plateaus at doses between 10-80 ug and optimization of the weight ratio of the components of the composition to provide an optimal response is well within the ordinary skill in the art and use the composition as modified supra for treatment of melanoma as taught by Livingston et al (Cancer Research). The Examiner stated that it also would have been *prima facie* obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined supra because they are all prominent cell-membrane components of melanomas as taught by Livingston et al (U.S. Patent No. 5,102,663) and one of ordinary skill in the art would react with the melanoma cells. The Examiner stated that it would have also been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GD3 lactone for the GM2 ganglioside in the composition because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990) and would be expected to product an enhanced antibody response as compared to GD3. The Examiner stated that optimization of the dosage, route to immunization, number of sites of immunization to

administer the composition is well within the skill of the ordinary artisan. The Examiner stated one would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and Uemura et al. (J Biochem, 79(6): 1253-1261,1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies. The Examiner stated that applicants' arguments have been carefully considered but are not persuasive. The Examiner stated applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation procedure as combined provides for the identical procedures as Applicant's coupling procedure. The Examiner stated moreover, the combination provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reducation of various sphingolipds did not affect the haptenic reactivity with antibodies. The Examiner stated applicants' have neither pointed distinguishing features of applicants invention nor provided any specific evidence or rationale which would indicate that the conjunction procedure as combined by the prior art would not arrived at the claimed product and methods. The Examiner stated applicants argument are not persuasive and the rejection stands across the new claims.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully disagree with the Examiner's contention that the conjugation procedure as combined provides for the identical procedure as applicants' coupling procedure. Applicants contend that the cited references, namely Livingston et al. (Cancer Research) in view of Ritter et al. (Seminars in Cancer

Biology), Liane et al (Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol), Kensil et al. (The Journal of Immunology), and Marciani et al. (Vaccine) and Uemura et al (J Biochem) does not teach, suggest or disclose applicants claimed invention and therefore do not render obvious the claimed invention.

Applicants point out that newly amended claim 78 which recites a composition which comprises: a) a conjugate of i) a GM2 or GD2 ganglioside derivative which comprises an unaltered oligosaccaride part and an altered ceramide portion, to ii) Keyhole Limpet Hemocyanin; b) a saponin derivable from the bark of a Quillaja saponaria Molina tree; and c) a pharmaceutically acceptable carrier; the relative amounts of such conjugate and such saponin being effective to stimulate or enhance antibody production in a subject, **wherein in the conjugate the ganglioside derivative is conjugated to Keyhole Limpet Hemocyanin through a ceramide-derived carbon of the ganglioside derivative to Keyhole Limpet Hemocyanin** [emphasis added].--

First, the Examiner acknowledges that the primary reference, i.e. Livingston et al. Cancer Research 1989, ("Livingston 1989") does not teach conjugation of GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on KLH in a composition or using this method for treatment (see June 19, 2000 Office Action, page 7).

To compensate for the lack of such disclosure, the Examiner relies relies primarily on two references, namely Ritter et al., Cancer Biology 1991 ("Ritter 1991") and Ritter et al., Immunobiology 1990

("Ritter 1990"). However, applicants submit that neither of these references supplies what it missing from the primary reference.

Ritter 1991 discloses on page 406, column 1 two approaches for augmenting the immunogenicity of gangliosides in a mouse, and states that only one of these approaches is capable of inducing consistent IgG antibodies to gangliosides in the mouse. Ritter 1991 describes this approach as covalently attaching gangliosides to foreign carrier proteins such as KLH.

Although Ritter 1991 refers to the conjugation of GM2 to KLH, there is no description of the chemical nature of the conjugate or of how to make the conjugate. Thus, Ritter 1991 neither discloses anything conjugated through the ceramide, nor enables making any such conjugate. Applicants respectfully direct the Examiner's attention to the highlighted portion of claim 97 above relating to the conjugation, which recites "...wherein in the conjugate the ganglioside derivative is conjugated to Keyhole Limpet Hemocyanin through a C-4 carbon of the sphingosine base of the ceramide portion of the ganglioside derivative to the ε-aminolysyl group of Keyhole Limpet Hemocyanin..." The Examiner's indication that one skilled in the art would interpret Ritter 1991 to involve ceramide conjugation is only speculation. Based on Ritter 1991, one skiiled in the art would not understand that the linkage would be through the ceramide. The Examiner tries to justify that the references teach linkages through the ceramide by using Ritter 1990. However, Ritter 1990 does **not** teach conjugation in a ceramide region.

Ritter 1990 describes making chemical derivatives of GD3. The four derivatives described in Table 1 on page 34 are as follows:

(1)amide, which is not immunoreactive with monoclonal antibodies to native GD3; (2) gangliosidol, which is not immunoreactive with monoclonal antibodies to native GD3; (3) lactone I, which is reactive but less than native GD3; and (4)lactone II, which is also reactive but less than native GD3. In Ritter 1990, there is no discussion of a conjugation to KLH. There is merely a description of chemical modifications of the ganglioside. Applicants point out to the Examiner that these derivatives are in the carbohydrate portion and not in the ceramide.

Based on the Table 4 in Ritter 1990, one would interpret that for GD3, the preference is to make a Lactone 1 derivative, which is a lactone chemically derivatized in the carbohydrate since it is more immunogenic than GD3 itself. Based on Ritter 1990, one would probably make a Lactone derivative. However, there is no suggestion of using the ceramide for such derivative.

The Examiner's attempt to use Ritter 1990 to support his obviousness speculation is incorrect because: (1) Ritter 1990 discloses that the conjugation is through the carbohydrate, not the ceramide; and (2) Ritter 1990 teaches away from ceramide conjugation and indicates that conjugation through a lactone is preferred.

Thus, there is neither a specific disclosure, nor is it obvious from either Ritter 1990 or Ritter 1991 to conjugate through the ceramide. Accordingly, the primary reference (i.e. Livingston et al.) in view of Ritter 1990 and Ritter 1991 does not teach, suggest or disclose the claimed invention Moreover, the other cited references do not supply what is missing from either the primary

reference, Ritter 1990 or Ritter 1991.

The Examiner cited Uemura et al as disclosing that ozonolysis and reduction of various sphingolipids do not affect the haptenic activity with antibodies. The Examiner stated that the combination [of references] provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies. However, Uemura et al does not supply what is missing from the primary reference with respect to conjugation through a ceramide-derived carbon to a carrier protein.

The Examiner cited Kensil and Marciani for their disclosures with respect to QS-21. The Examiner cited Livingston et al. (U.S. Patent No. 5,102,663) with respect to various gangliosides being cell membrane components of melanoma. Accordingly, neither of these references disclose what is missing from the primary reference with respect to conjugation through a ceramide-derived carbon to a carrier protein.

The Examiner cited Liane et al (Journal of Biological Chemistry), alleging that it "teaches a method for covalent coupling of gangliosides to amino ethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the spingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group bearing glass beads." Applicants submit that Liane does not supply what is missing from the primary reference with respect to conjugation through a ceramide-derived carbon. In support, applicants attach hereto as **Exhibit B** a copy of Helling et al.,

Cancer Research 54: 197-203, which was cited as reference 3 in an information disclosure statement filed on May 2, 1997 in connection with the subject application. Applicants point out that Helling et al. addresses the cited reference (i.e. Liane et al.) on page 201, second paragraph of the discussion stating the "earlier" Liane et al. method

> is of limited use for the conjugation of gangliosides to carrier proteins because it requires acetylated, methyl ester derivatives of gangliosides to avoid coupling via the sialic acid carboxyl group. Deacylation after conjugation under basic conditions is necessary, conditions most proteins cannot be exposed to without degradation.

Applicants point out that the claimed invention recites in part "...a conjugate of i) a GM2 or GD2 ganglioside derivative which comprises an unaltered oligosaccaride part and an altered ceramide portion, to ii) Keyhole Limpet Hemocyanin..." Keyhole Limpet Hemocyanin is a carrier protein and accordingly, the Liane et al. methods would not enable a conjugation such as that recited in the claims because the Liane et al. conditions would result in protein degradation. Accordingly Liane et al. does not provide what is missing from the primary reference, i.e. a teaching of a conjugation of a ganglioside to a protein through a ceramide derived carbon, and an enabling disclosure of how to do so. Therefore, the primary reference in view of Liane et al. does not teach, suggest or disclose the claimed invention.

Accordingly, the primary reference, i.e. Livingston 1989 in view of the other cited references, namely Ritter 1990, Liane et al (Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter 1991, Kensil et al. (The Journal of

Immunology), and Marciani et al. (Vaccine) and Uemura et al (J Biochem) does not render obvious the applicants' claimed invention. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claim 95 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261,1976) as applied to claims 78-94 and 96-99 above and further in view or Irie et al. (U.S. Patent No. 4,557,931) is maintained for reasons made of record for claim 67, in Paper No. 23, mailed 10-5-99. The Examiner stated the teachings of Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani er al., and Uemura et al (Jbiochem, 79(6):1253-1261, (1976) are set forth supra. The Examiner stated that the combination differs by not teaching the administration of the composition for treating cancer of epithelial origin. The Examiner stated Irie et al teaches that the ganglioside GM2 is found on or in tumors of a variety of historical types including melanoma and breast carcinomas (column 1, lines 28-31). The Examiner stated it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the GM-2-KLH conjugate/QS-21

composition or other ganglioside conjugate/QS-21 composition as combined *supra* to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Ire et al and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

The Examiner stated applicants' argument have been carefully considered but are not persuasive. The Examiner stated applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation procedure as combined provides for the identical procedure as Applicants' coupling procedure. The Examiner stated Moreover, the combination provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipds did not affect the haptenic reactivity with antibodies. The Examiner stated applicants' have neither pointed distinguishing features of applicants invention nor provided any scientific evidence or rationale which would indicate that the conjugation procedure as combined by the prior art would not arrived at the claimed product and methods. The Examiner stated applicants arguments are not persuasive and the rejection stands across the new claims.

In response, applicants respectfully traverse the Examiner's above rejection for the reasons stated above supra on pages 14-20. Applicants contend that Irie does not supply what is missing from either the primary reference or any of the other references, i.e. with respect to conjugation of gangliosides through a ceramide-

derived carbon to carrier proteins. Accordingly Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem) as applied to claims 69-81 and 83-96 above and further in view of Irie et al. (U.S. Patent No. 4,557,931) does not teach, suggest or disclose applicants' claimed invention and therefore do not render obvious the claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 78-92 and 94-99.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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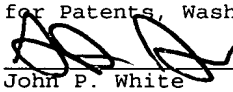
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



7-19-01

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